40. (Amended) The method ~~of~~ claim 37 wherein the resistance test vector comprises genes encoding C, E1, E2, NS2, NS3, NS4, or NS5 proteins of HCV. ~~c~~

REMARKS

Claims 1, 4, 8, 20, 25, 37, 40, 55-59, 62, 77, 91, 94 and 108-111 are pending and in this application. Claims 20, 25, 59, 62, 77, 91, 94, and 108-111 have been withdrawn from consideration by the Examiner. Applicants have amended the specification to the correct informalities. Applicants have amended claims 1, 4, 8, 37, and 40. Support for the amendments can be found, inter alia, on page 6, lines 5-9, page 16, lines 21-28, page 32, lines 10-14, page 19, lines 28-30, and on page 22, lines 5-7 and lines 16-20. The amendments raise no issue of new matter. Applicants request the entry of this Amendment. Upon entry of this Amendment, claims 1, 4, 8, 37, 40 and 55-58 will be under examination.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1, 4, 8, 37, 40, and 55-58 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that claims 1 and 37 are drawn to methods for determining susceptibility for an HCV antiviral drug which comprises introducing a resistance test vector comprising a patient-derived segment which comprises a hepatitis C virus (HCV) gene and an indicator gene into a host cell. The Examiner stated that the preamble of each of the claims is unclear as to what is being tested for susceptibility. The Examiner stated that for clarification, it is suggested that "for" be deleted from line

1 in each of the claims and that a phrase such as "of a hepatitis C virus strain" or "of a patient-derived viral strain" or other comparable phrase be inserted in line 1 after "susceptibility" for clarification.

The Examiner stated that claims 1 and 37 are incomplete for omitting essential steps, such omission amounting to a gap between the steps. The Examiner stated that the omitted steps are measuring expression of the indicator gene in a target cell in the absence of an HCV antiviral drug and a correlation step. The Examiner stated that the syntax of the claim renders the sequence of steps confusing because it is not clear what is to be compared. The Examiner stated that additionally, it is unclear how in step (c) expression of the indicator gene in a target cell in the presence of an antiviral drug can be measured if the drug is not present in either steps (a) and (b) or in step (b). The Examiner stated that it is suggested that the claim be amended to recite something such as,

> (c) measuring expression of the indicator gene in a target cell in the absence of an HCV antiviral drug;
>
> (d) measuring expression of the indicator gene in a target cell, wherein an HCV antiviral drug is present at steps(a)-(b) or at step (b); and
>
> (e) comparing the expression of the indicator gene from (d) with the expression of the indicator gene from (c),
>
> wherein a reduction in expression of the indicator gene in (d), as compared to (c), is indicative of susceptibility to the antiviral drug.

In response, without conceding the correctness of the Examiner's position but solely to advance prosecution, the applicants have amended claims 1 and 37 to recite that the expression of the

indicator gene is dependent upon the patient derived segment during the measuring step (c). Support for the amendment can be found, inter alia, on page 16, lines 21-28 and page 32, lines 10-14.

The applicants respectfully traverse the Examiner's rejection of claims 1 and 37 based on the preamble being unclear. It is clear from the specification that "susceptibility for an HCV antiviral drug" as stated in the preamble specifically refers to "viral drug susceptibility" as it is defined in the specification on page 40, lines 13-19. Viral drug susceptibility is clearly defined as "the concentration of the antiviral agent at which a given percentage of indicator gene expression is inhibited." Applicants submit that indicator gene expression is sufficiently described in the context of the specification to render the meaning of the preamble of claims 1 and 37 clear to one skilled in the art as applying to susceptibility of an HCV viral segment to an HCV antiviral drug. Accordingly, the applicants respectfully request the Examiner withdraw this ground of rejection.

The applicants submit that claims 1 and 37 as amended, do not omit the two essential steps cited by the Examiner of: 1) measuring the expression of the indicator gene in a target sell in the absence of an HCV antiviral drugs, and 2) a correlation step.

First, step (d) of claims 1 and 37 states in part "... the expression of the indicator gene measured when steps (a)-(c) are carried out in the absence of the HCV antiviral drug." Clearly, there is a measurement of the expression of the indicator gene in the absence of the HCV antiviral drug as required by the

Examiner.

Second, the operational connection or correlation between the patient-derived segment and the indicator gene recited in claims 1 and 37, wherein the expression of the indicator gene is dependent upon the patient derived segment during the measuring step (c), sufficiently characterizes the essence of the claimed methods because the specification explicitly describes that "in each case, the expression of the indicator gene in the target cell is ultimately dependent upon the action of the patient-derived segment." (See page 32, lines 10-14). The specification discloses that comparison of expression of the indicator gene in the presence of an anti-viral agent, as compared to expression in the absence of an anti-viral agent, allows calculation of the inhibitory concentration (IC) for the viral target product encoded by the patient derived segment. (See page 44, lines 4-19). Therefore the change in expression intensity for the indicator gene will depend upon the patient-derived segment. The operational connection between the patient-derived segment and the indicator gene is what determines the IC for the patient-derived viral segment and, therefore, characterizes the method for determining susceptibility for an HCV anti-viral drug. Consequently, the applicant respectfully maintains that amended claims 1 and 37 comply with §112, Second Paragraph.

The applicants also submit that the expression of the indicator gene in measuring step (c) can be measured if the anti-viral drug is not present in either steps (a) and (b), or in step (b). In Example 1, the specification on page 57, lines 30-33, states "at the time of transfection or infection, depending on the drug target, the appropriate concentration of the antiviral drug is added to the host or target cell cultures. The Examiner is

directed to the specification on page 40, line 32 to page 42, line 10, where it is noted that there are at least two types of drug susceptibility tests according to the present invention. In the first type, viral particles are produced by a first host cell which are then used to infect a second host cell (the target host cell). In the second type, a single host cell also serves as a target host cell. However, in either case where a functional or nonfunctional indicator gene is used, efficient expression of the indicator gene occurs when infection of a target host cell occurs. See page 41, lines 10-14 and lines 30-35. Since, in Example 1 the anti-viral drug may be added during infection of the target cell cultures, it is clear from the method as claimed that this could occur during step (c) where a target host cell is present to measure the expression of the indicator gene. The specification on page 44, lines 9-19 clearly indicates that drug susceptibility can be calculated by noting the reduction in luciferase activity observed for target host cells infected with viral particles in the presence of a given antiviral agent, as compared to a control run in the absence of the antiviral agent. Accordingly, the applicants respectfully request the Examiner withdraw this ground of rejection.

The Examiner stated that claims 4 and 40 recite genes encoding C, E1, E2, NS2, NS3, NS4, or NS5. The Examiner stated that it is suggested for clarification that the claim be amended to insert --proteins of HCV -- at the end of the claim. The Examiner stated that it is also suggested that claim 1 be amended to insert --(HCV)-- in line 5 immediately after "hepatitis C virus" and that all subsequent occurrences of hepatitis C virus be changed to HCV for consistency (see claim 37, line 5).

The Examiner stated that claim 8 recites "IRES". The Examiner

stated that immediately preceding the first occurrence of the acronym, the full name --internal ribosome entry site— should be inserted with parentheses around the abbreviation.

The Examiner stated that claim 8 is rejected as depending from a canceled claim. The Examiner stated that correction is required. The Examiner stated that it is suggested that claim 8 either be canceled or rewritten in independent form incorporating all limitations of the base claims or that claim 8 be rewritten to recite the limitations of claim 5 and to depend from claim 1. The Examiner stated that for purpose of examination, claim 8 has been interpreted to include all limitations of base claim 1 and canceled claim 5.

In response, without conceding the correctness of the Examiner's position but solely to advance prosecution, the applicants have amended claims 1, 4, 37 and 40 by inserting the abbreviation "HCV" after hepatitis C virus". Claim 8 is amended to depend on claim 1, and include the limitations of canceled claim 5, and also to insert the phrase "internal ribosome entry site" before "IRES" as suggested by the Examiner.

Applicants submit these amendments obviate this ground of rejection and respectfully request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner stated that claims 1, 4, 8, 37, 40 and 55-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determination of antiviral drug susceptibility wherein the antiviral drug is present in steps(a) and (b) or in step (b), does not reasonably

provide enablement for determination of antiviral drug susceptibility when the drug is present only at step (c). The Examiner stated that step (c) is drawn to measuring expression of the indicator gene in a target host cell; without the antiviral drug being present in either step (a) wherein the resistance test vector is introduced into the host cell or in step(b) wherein the host cell is cultured, one of skill in the art would be unable to measure a reduction in expression of the indicator gene in step (c). The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In reply, applicants respectfully traverse the Examiner's rejection of claims 1, 4, 8, 37 and 55-58 as not enabled for determination of antiviral drug susceptibility when the antiviral drug is present only at step (c). As stated above, it is clear from Example 1 in the specification on page 57, lines 30-33, that "at the time of transfection or infection, depending on the drug target, the appropriate concentration of the antiviral drug is added to the host or target cell cultures. The Examiner is directed to the specification on page 40, line 32 to page 42, line 10, where it is noted that there are at least two types of drug susceptibility tests according to present invention. In the first type, viral particles are produced by a first host cell which are then used to infect a second host cell (the target host cell). In the second type, a single host cell also serves as a target host cell. However, in either case where a functional or nonfunctional indicator gene is used, efficient expression of the indicator gene occurs when infection of a target host cell occurs. (See page 41, lines 10-14 and lines 30-35). Since, in Example 1 the anti-viral drug may be added during infection of

the target cell cultures, it is clear from the method as claimed that this could occur during step (c) where a target host cell is present to measure the expression of the indicator gene. The specification on page 44, lines 9-19 clearly indicates that drug susceptibility can be calculated by noting the reduction in luciferase activity observed for target host cells infected with viral particles in the presence of a given antiviral agent, as compared to a control run in the absence of the antiviral agent. The specification notes that such reduction in luciferase activity relates to the log of the concentration of the antiviral agent as a sigmoidal curve, which is used to calculate the IC concentration of the antiviral agent. (See page 44, lines 9-19). Furthermore, Figures 1-17 specifically diagram the HCV genome structure and the particular resistance test vectors and plasmid diagrams, including indicator genes, such that one skilled in the art would be enabled to practice the invention in view of the teachings of the specification. Accordingly, the applicants respectfully request the Examiner withdraw this ground of rejection.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 1, 4, 8, 55 and 57 under 35 U.S.C. §103(a) as being unpatentable over Gerna et al., ("Rapid Screening for Resistance to Ganciclovir and Foscarnet of Primary Isolates of Human Cytomegalovirus from Culture-Positive Blood Samples", J. Clin. Microbiol. 33:738,1995), in view of Lu et al., ("Poliovirus Chimeras Replicating under the Translational Control of Genetic Elements of Hepatitis C Virus Reveal Unusual Properties of the Internal Ribosomal Entry Site of Hepatitis C Virus", PNAS 93:1412, 1996), and Wang et al., ("Translation of Human Hepatitis C Virus RNA in Cultured Cells Is Mediated by an Internal Ribosome-Binding Mechanism", J. Virol. 67:3338, 1993).

The Examiner stated that the claimed invention is drawn to a method for determining susceptibility of an HCV strain for an antiviral drug comprising introducing a resistance test vector comprising a patient-derived HCV gene and an indicator gene in to a host cell, culturing the host cell, and comparing expression of the indicator gene in the presence of an antiviral drug with expression in the absence of the drug. The Examiner stated that dependent claims recite the additional limitations of the resistance test vector comprising genes encoding the C, E1, E2, NS2, NS3, NS4 or NS5 proteins of HCV; the patient-derived HCV gene comprising an internal ribosome entry site (IRES); and recite methods for determining HCV antiviral drug resistance in an infected patient comprising developing a standard curve of drug susceptibility for the antiviral drug and comparing the measured susceptibility to the standard curve as an indication of HCV antiviral drug resistance in the HCV-infected patient, or by comparing HCV antiviral drug susceptibilities in the same patient measured at a first and a later time as an indication of the development or progression of viral drug resistance in the patient.

The Examiner stated that Gerna et al. teaches methods for determining susceptibility of human cytomegalovirus (HCMV) to antiviral drugs. The Examiner stated that Gerna et al. teach conventional methods for determination of drug susceptibility as comprising a plaque reduction assay in susceptible cell culture (immediate early antigen or IEA plaque assay) in the presence of the antiviral drug (ganciclovir or foscarnet) and comparison of the titer of the virus to a standard curve of drug susceptibility determined from control virus strains (see the entire document and especially page 738, the paragraph bridging columns 1 and 2 and the first sentence of the second paragraph in column 2). The

Examiner stated that Gerna et al. teaches that antiviral drug susceptibility testing is important because the use of antiviral agents can result in emergence of drug-resistant virus strains (see page 738, first paragraph). The Examiner stated that the methods described by Gerna et al. differ from the claimed methods in that they do not teach determination of drug susceptibility for HCV and they do not teach the use of resistance test vectors.

The Examiner stated that Lu et al. teaches that HCV does not replicate in cell cultures to any appreciable titer. The Examiner stated that Lu et al. teaches that this has hindered efforts to develop HCV-specific antiviral drugs (see page 1412, column 2, second paragraph). The Examiner stated that Lu et al. teach that certain RNA viruses, including HCV, have developed the mode of translation by IRES elements, which allows entry of the translational machinery into mRNAs without recognition of a 5'-end cap structure (see the paragraph bridging pages 1415 and 1416). The Examiner stated that Lu et al. teaches that a chimeric polio/HCV virus which incorporates the HCV IRES, an HCV core (C) segment, and poliovirus segments productively infects cell culture, thereby allowing for HCV antiviral drug testing. The Examiner stated that Lu et al. teach that the use of the chimeric virus, however, is limited to detection of HCV antiviral agents which target the 5'NTR or core protein (see page 1412, column 2, third paragraph).

The Examiner stated that Wang, et al. teaches methods for construction of vectors incorporating HCV-derived segments which comprise an IRES and an indicator gene (chloramphenicol acetyltransferase [CAT] or luciferase [LUC]) (see pages 3338, *Materials and Methods*, first three paragraphs). The Examiner stated that Wang et al. teach introduction of the HCV-derived

segments into cells by transfection, incubation of the transfected cells in culture, and measurement of expression of the indicator gene as indicative of viral translation (see page 3339, column 2, third full paragraph; page 3340, column 2, last paragraph; and page 3341, column 1, first paragraph).

The Examiner stated that one of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have used the transfection methods taught by Wang et al. as a substitute for the plaque reduction assay taught by Gerna et al., in order to enable HCV antiviral susceptibility testing, either for elucidation of new HCV antiviral agents, as suggested by Lu et al., or for determination of drug susceptibility or developing resistance in a particular patient, as suggested by Gerna et al. The Examiner stated that one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the methods taught by Wang, rather than the chimeric virus taught by Lu et al., in order to expand testing to antiviral agents in addition to those which target the 5'NTR ro C protein of HCV.

The Examiner rejected claims 37, 40, 56 and 58 under 35 U.S.C. §103(a) as being unpatentable over Gerna et al. in view of Lu et al. and Wang et al., as applied to claims 1, 4, 8, 55 and 57 above, and further in view of Hirowatari et al.

The Examiner stated that the claimed invention is drawn to a method for determining susceptibility of an HCV strain for an antiviral drug comprising introducing a resistance test vector comprising a patient-derived HCV gene and a nonfunctional indicator gene into a host cell, culturing the host cell, and comparing expression of the indicator gene in the presence of an

antiviral drug with expression in the absence of the drug. The Examiner stated that dependent claims recite the additional limitations of the resistance test vector comprising genes encoding the C, E1, E2, NS2, NS3, NS4 or NS5 proteins of HCV and methods for determining HCV antiviral drug resistance in an infected patient comprising developing a standard curve of drug susceptibility for the antiviral drug and comparing the measured susceptibility to the standard curve as an indication of HCV antiviral drug resistance in the HCV-infected patient, or by comparing HCV antiviral drug susceptibilities in the same patient measured at first and later times as an indication of the development or progression of drug resistance in the patient.

The Examiner stated as described *supra,* Gerna et al. teach methods for determining resistance to an antiviral drug comprising determining the susceptibility of a patient-derived isolate to the antiviral drug and comparison of the determined susceptibility to a standard curve. The Examiner stated that Lu et al. teach methods for testing HCV isolates in otherwise nonpermissive cells by incorporation of the HCV IRES element and C protein with poliovirus segments into a chimeric virus. The Examiner stated that Wang et al. teach methods of construction of vectors comprising HCV segments which include the IRES element and an indicator gene, transfection of cells with the vectors, incubation of the transfected cells, and measurement of expression of the indicator gene. The Examiner stated that the claimed invention differs from the methods of Gerna et al. in view of Lu et al. and Wang et al. in the recitation of a nonfunctional indicator gene. The Examiner stated that a nonfunctional indicator gene is understood to mean one which is not efficiently expressed in a packaging host cell transfected with the resistance test vector until it is converted into a

functional indicator gene through the action of one or more of the patient-derived HCV segment products, as is defined at page 33, lines 3-12, of the disclosure.

The Examiner stated that Hirowatari et al. teach a method for testing antiviral activity of HCV proteinase inhibitors comprising construction of plasmids encoding a reporter gene, the proteinase enzyme gene, and the substrate gene which are simultaneously transfected into cells in culture. The Examiner stated that Hirowatari et al. teach the reporter plasmid as containing the CAT gene downstream of an enhancer/promoter sequence derived from human T-cell leukemia virus type 1 (HTLV-1) long terminal repeat(LTR). The Examiner stated that Hirowatari et al. teach the substrate expression plasmid as a triple chimera comprising HCV NS2, the substrate polypeptide, and the Tax 1 protein of HTLV-1. The Examiner stated that Hirowatari et al. teach that the Tax 1 transactivates the expression of the CAT gene through the enhancer sequence of HTLV-1 LTR only after it is released from the chimera by HCV proteinase-dependant cleavage (see page 113, abstract, and the paragraph bridge pages 114 and 115). The Examiner stated that Hirowatari et al. teach that this system allows for safe *in vivo* testing of antiviral agents without risk of exposure to infectious, pathogenic virus (see page 113, the paragraph bridging columns 1 and 2).

The Examiner stated that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used a nonfunctional indicator gene, as taught by Hirowatari et al., as the indicator gene in the methods taught by Gerna et al. in view of Lu et al. and Wang et al;, as an alternative indicator of viral susceptibility to antiviral agents without the potential for hazardous exposure to infectious virus.

In reply, applicants respectfully traverse the rejection under 35 U.S.C. §103 over Gerna et al., in view of Lu et al. and Wang et al.

Applicant's Invention

Applicant's claimed invention is directed to a method for determining susceptibility for an HCV anti-viral drug comprising: (a) introducing a resistance test vector comprising a patient-derived segment which comprises a hepatitis C virus (HCV) gene and an indicator gene into a host cell; (b) culturing the host cell from (a); (c) measuring expression of the indicator gene in a target host cell, wherein the expression of the indicator gene is dependent upon the patient-derived segment; and (d) comparing the expression of the indicator gene from (c) with the expression of the indicator gene measured when steps (a)-(c) are carried out in the absence of the (HCV) anti-viral drug, wherein a test concentration of the HCV anti-viral drug is present at steps (a)-(c); at steps (b)-(c); or at step (c).

Gerna et al.

Gerna et al. describes the use of a rapid assay for the detection of decreased susceptibility of HCMV to foscarnet and ganciclovir. The assay is based on an immediate-early antigen (IEA) plaque reduction assay (PRA) using isolated whole virus from a patient. The cell culture systems used with HCMV allow for the growth of intact HCMV in culture. Gerna et al. neither suggests nor describes the construction of a resistance test vector comprising a patient derived segment and a reporter. Furthermore, the rapid assay described in Gerna et al. does not give an accurate measure of the level of drug susceptibility, but rather simply an indication of "resistant" or "sensitive." In other words, the methods of Gerna et al. do not allow for the quantitation of

susceptibility. The Gerna et al. method neither describes nor suggests the recombinant method of introducing a resistance test vector comprising a patient derived segment of a hepatitis C virus with an indicator gene, wherein expression of the indicator gene is linked to the patient derived segment. Furthermore, the Gerna et al. method neither describes nor suggests a method which provides the quantitative susceptibility data for determining susceptibility for an HCV anti-viral drug as with the applicants' invention.

Lu et al.

Lu et al. describes an HCV internal ribosome entry site (IRES)/core-poliovirus (PV) chimeric that could be used for basic research into the function of the HCV IRES and as a screening tool for anti-HCV IRES drugs, but does not provide a quantitative method for determining susceptibility for an HCV anti-viral drug according to the applicants' invention. Lu et al. does not suggest nor teach the recombinant method of introducing a resistance test vector comprising a patient derived segment of a hepatitis C virus with an indicator gene, wherein expression of the indicator gene is linked to the patient derived segment. The chimeric vector of Lu et al. contains only two portions of the HCV genome, the IRES and 366 nt of the HCV core coding sequence downstream of the HCV 5' NTR. The chimeric virus of Lu et al. does not teach nor suggest, and would not enable an analysis of the resistance or susceptibility of a patient infected with Hepatitis C. The chimeric vectors of Lu et al. would not be useful for research or screening with respect to compounds targeting other regions of HCV which are currently more likely targets for drug development e.g. NS3 protease or helicase or NS5B RNA-dependent RNA polymerase. In addition, the behavior of an RNA functional element such as an IRES is highly dependent

on the context in which it is found. Therefore it is possible that the response of the IRES to anti-HCV IRES compounds in the context of an HCV/PV chimera would not give an accurate measurement of the activity of the compound against intact HCV. In addition, using the HCV/PV chimera of Lu et al. to produce plaques precludes the substitution of PV proteins with any of those of HCV, since all of the PV proteins are required for productive infection and plaque generation. Moreover, the HCV/PV chimera of Lu et al. does not suggest nor teach the recombinant method of introducing a resistance test vector comprising a patient derived segment of a hepatitis C virus with an indicator gene, wherein expression of the indicator gene is linked to the patient derived segment.

Wang et al.

Applicants contend that Wang et al. was one of the first to describe the ability of the HCV 5' non-coding region to promote internal initiation of translation, by placing the translation of a reporter gene under the control of the HCV IRES. The recombinant plasmids of Wang et al. contain the 5' noncoding sequences of HCV but do not contain the genes encoding the more likely drug targets. This work, while helping to lay the foundation for the understanding of the mechanism by which HCV RNA's are translated, is subject to the same drawbacks of Lu et al. in that it takes the HCV IRES out of its natural context and does not provide the recombinant method of introducing a resistance test vector comprising a patient derived segment of a hepatitis C virus with an indicator gene, wherein expression of the indicator gene is linked to the patient derived segment. The Examiner states that it would have been obvious to take the transfection methods taught by Wang et al. (RNA transfection into cultured cells using lipids) and the plaque reduction assay taught by Gerna et al. (inhibition of plaque formation by HCMV

in cells) to enable HCV antiviral susceptibility testing. Further, the Examiner states that the methods taught by Wang et al. (RNA transfection of reporter genes under control of the HCV IRES) could be used instead of the HCV/PV chimera approach of Lu et al. to expand susceptibility testing to those which target regions of HCV besides the IRES.

However, in response, the applicants submit that: (a) the plaque reduction assay of Gerna et al. does not provide quantitative information about the level of drug susceptibility to determine the susceptibility for an HCV anti-viral drug as claimed by the applicants; (b) the RNA transfection of constructs which more closely resemble HCV do not produce plaques which can be counted and in therefore do not provide a method for determining HCV anti-viral drug susceptibility; and (c) using the HCV/PV chimera to produce plaques precludes the substitution of PV proteins with any of those of HCV, since all of the PV proteins are required for productive infection and plaque generation, and thus provides no suggestion for a resistance test vector comprising a patient derived segment of a hepatitis C virus with an indicator gene.

Applicants maintain that Gerna et al. in view of Lu et al. and Wang et al., alone or in combination, do not teach or suggest the linkage of patient-derived sequences to the reporter gene as part of an HCV-like replicating virus for determining HCV anti-viral drug susceptibility of the applicants' claimed invention. Furthermore, there is no suggestion in any of the references for their combination, as the Examiner concedes that Gerna et al. does not suggest a method for determination of drug susceptibility for HCV; Lu et al. teaches the use of a specific chimeric polio/HCV virus for

drug screening, but not necessarily a method useful for determination of drug susceptibility; and Wang et al. identifies use of an expression vector to identify a particular HCV region (5' NCR) involved in HCV translation.

Applicants further submit that even if there was a suggestion to combine all of the references cited by the Examiner, their combination would not yield the applicants invention as claimed. Combination of the cited references does not provide a recombinant method of introducing a resistance test vector comprising a patient derived segment of a hepatitis C virus with an indicator gene, wherein expression of the indicator gene is linked to the patient derived segment to quantitatively determine antiviral drug susceptibility. Accordingly, the applicants respectfully request the Examiner withdraw this ground of rejection.

Applicants respectfully traverse the rejection under 35 U.S.C. §103 over Gerna et al., in view of Lu et al. and Wang et al., and in further view of Hirowatari et al., ("A Novel Method for Analysis of Viral Proteinase Activity Encoded by Hepatitus C Virus in Cultured Cells",Anal. Biochem. 225:113, 1995).

Hirowatari et al.

Hirowatari et al. describes the use of HCV NS2 and NS3 protease-HTLV-[tax] transcription trans-activator chimeras to monitor the activity of the NS2 protease in cultured cells. HCV protease-dependent cleavage of the chimera releases tax 1 which can then migrate to the nucleus and activate expression of a reporter gene. However, Hirowatari et al. does not teach or suggest the transfer of patient derived sequences into the chimeras as claimed by the

applicants, which may be required in order to test for HCV protease inhibitor susceptibility of a patient's virus. Moreover, as with Lu et al. and Wang et al., this method does not use the entire HCV gene thus failing to enable the assessment of other drug targets such as helicase, protease or polymerase.

The Examiner stated, "Lu et al. teach methods for testing HCV isolates in otherwise nonpermissive cells..." Applicants submit that as described above, Gerna et al., in view of Lu et al. and Wang et al., do not address the testing of patient-derived sequences and do not provide for testing the activity of non-structural HCV proteins. Furthermore, there is no suggestion to combine Gerna et al., in view of Lu et al. and Wang et al., in further view of Hirowatari et al. for the reasons described above, and because Hirowatari et al. describes the use of HCV NS2 and NS3 protease-HTLV-[tax] transcription trans-activator chimeras to monitor the activity of the NS2 protease in cultured cells, but not necessarily a specific method useful for determination of drug HCV susceptibility.

Applicants further submit that even if there was a suggestion to combine all of the references cited by the Examiner, their combination would not yield the applicants invention as claimed. Combination of the cited references does not provide a recombinant method of introducing a resistance test vector comprising a patient-derived segment of a hepatitis C virus with an indicator gene, wherein expression of the indicator gene is linked to the patient derived segment to quantitatively determine antiviral drug susceptibility. Accordingly, the applicants respectfully request the Examiner withdraw this ground of rejection.

CONCLUSION

The applicants respectfully submit that the present amendments and accompanying remarks serve to place the claims in condition for allowance.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone the attorney at the number provided below.

No fee, other than the enclosed $435.00 for an extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Jane M. Love

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents Washington, D.C. 20231.

Jane M. Love 7/10/00

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